PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Aminoacetonitriles, their preparation and Compositions containing them

We, KYORIN SEIYAKU KABUSHIKI KAISHA, a Japanese Corporate Body, of No. 6, 4-chome, Nihonbashi-Honcho, Chuo-Ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with improvements in or relating to aminoacetonitriles, their preparation and compositions containing them, and is in particular concerned with N-amino-acyl-aminoacetonitriles of improved physiological value.

Aminoacetonitrile itself (that is, the compound of the structural formula $NH_2.CH_2CN$) not only has valuable medical properties in that it prevents liver damage caused by materials such as carbon tetrachloride, bromobenzene and thioacetamide, but it is also capable of enhancing liver regeneration and preventing liver cirrhosis. Nevertheless, it has harmful pharmacodynamic effects on the vermiculation of intestines, and has strong influences on both the heart rate and the blood pressure, so that it is of little value in clinical practice.

N-Amino-acid derivatives of aminoacetonitrile (that is, compounds of the general formula:

$$H_2N.R.CO.NH.CH_2CN$$

wherein $H_2N.R.CO$ is the basic structure of amino-acids $H_2N.R.COOH$ and R is a substituted or unsubstituted hydrocarbon group), also protect the liver to the same extent as aminoacetonitrile itself, and moreover are only about one-tenth as virulent pharmacodynamically. Thus, they are useful in clinical practice.

Even so, some interesting facts have been found from studying the N-amino-acyl-aminoacetonitriles biochemically. In particular it has been found that the so-called lathylogenic substance present in sweet-pea causes denaturation (liquescence) of acid muco-polysaccharides which are components of the cartilage of young animals, thus causing denaturation of cartilages and, in addition, suppressing the propagation of fibrinous cells. Furthermore, it is known that aminoacetonitrile itself is a substance having an especially strong lathyrogenic activity.

In conducting these investigations it has also been found that the correlation between the valuable liver protecting activity and the harmful pharmacodynamic and lathylogenic activities can be altered so that the harmful effects are reduced and the valuable properties are then available substantially unimpaired for use in the medical treatment of human disorders and diseases. Specifically it has been found that the harmful secondary effects of N-amino-acyl-aminoacetonitriles may be reduced without substantially altering their liver protecting properties by acylation of the terminal amino group.

Accordingly, in one aspect, the present invention provides N-(acyl-amino-acyl)-aminoacetonitriles of the general formula:

$$R'.CO.NH.R.CO.NH.CH_2CN$$

wherein NH.R.CO is as defined hereinbefore, and R' is a straight or branched alkyl, aryl or aralkyl group.

The amino-acid group NH.R.CO may be derived from any convenient amino-acid. Thus, by way of example only, it may be derived from glycine, α-alanine, β-alanine, α-aminobutyric acid, α-amino-iso-butyric acid, valine, leucine, isoleucine, norleucine, methionine, lysine, tryptophane, α-, β-, γ, δ- or ε-aminocaproic acid, aspartic acid, phenylalanine, tyrosine, phenyl-glycine, or δ-aminovaleric acid.

[*Price* 4*s*. 6*d*.]

Similarly, the group R′ may be any of those alkyl, aryl or aralkyl groups commonly found in pharmacologically active materials. It contains preferably not more than 18 carbon atoms, and advantageously from 1 to 9 carbon atoms. Specifically preferred groups are the methyl, ethyl, propyl, i-propyl, butyl, pentyl, hexyl and phenyl groups.

The particular value of the N-(acyl-amino-acyl)-aminoacetonitriles of the invention may be illustrated by reference to the following Table.

	Liver Protecting & antidotal activities	Suppressing effect on intestinal vermiculation	Lathylogenic activity
Aminoaceto-nitrile	Strong	Strong	Very strong
Amino-acid-aminoaceto-nitriles	Equal to that of aminoaceto-nitrile	1/10 of that of amino-acetonitrile	Half of that of aminoaceto-nitrile
Acyl-amino-acid-aminoaceto-nitriles	Equal to that of aminoaceto-nitrile	Less than 1/10 of that of aminoaceto-nitrile	Less than 1/4 of that of aminoaceto-nitrile

It is to be noted that the prevention of liver cirrhosis, that is fibrination, is not suppressed by reduction of the lathylogenic activity, and thus, in cases where priority is to be given to the functioning of the liver, for example, in cases where it is desired to prevent liver disorders caused by inspirated anesthesia, blood transfusions and so on, a lower lathylogenic activity is advantageous. Consequently the compounds of the present invention are particularly useful. Nevertheless, for the prevention of the liver cirrhosis tendency alone, the amino-acid-aminoacetonitriles may still be of value.

That the acylated compounds of the present invention are particularly valuable will now be more fully illustrated by reference to the accompanying drawings in which:—

Figures 1 and 2 are graphs demonstrating the pharmacological value of N-(N-acetyl-glycyl)-aminoacetonitrile in preventing the liver damage which can be caused by carbon tetrachloride.

When the parenchyma of the liver is disrupted, for example, upon injection of carbon tetrachloride into mice, the enzymes glutamic oxaroacetic transaminase and glutamic pyruvic transaminase are released in large amounts into the blood serum, as shown by the dotted lines in each of the graphs. Moreover, it has been established by various experiments that the relative absence of the enzymes from the blood serum is indicative of no disorder in the parenchyma of the liver, so that the concentration of the enzymes in the blood serum may be taken as a reliable method for the diagnosis of liver disorder. Thus, when N-(N-acetyl-glycyl)-aminoacetonitrile is administered at the same time as carbon tetrachloride to mice, and the concentration of the two enzymes in the blood serum is found to remain substantially constant, as shown by the continuous lines in each of the graphs, it is clear that the nitrile is preventing liver damage.

According to the present invention, in another aspect, the N-(acyl-amino-acyl)-aminoacetonitriles may be prepared by reacting an N-amino-acyl-aminoacetonitrile with an acylating agent so as to form the corresponding N-acyl-amino-derivative.

The acylating agent may be an acid anhydride or acyl halide, these two reactions taking place according to the respective equations:

(i) $H_2N.R.CO.NH.CH_2.CN + (R'CO)_2O \rightarrow R'.CO.NH.R.CO.NH.CH_2.CN$

(ii) $H_2N.R.CO.NH.CH_2.CN + R'CO.Ha \rightarrow R'.CO.NH.R.CO.NH.CH_2.CN$

(wherein R and R′ are each as defined hereinbefore, and Ha is a halogen atom)

When the acylating agent is an acid anhydride, the reaction is readily effected without a solvent or in the presence of a solvent, for example, in an aqueous medium. The anhydride may be, for example, acetic anhydride, propionic anhydride, butyric anhydride, isobutyric anhydride and so on.

When the acylating agent is an acyl halide, the halogen atom is desirably the bromine or chlorine atom, whilst it is particularly advantageous for there to be present in the reaction mixture an acid binding agent such as sodium bicarbonate, sodium carbonate, potassium carbonate, pyridine or triethylamine. Conveniently, the reaction is effected in an aqueous medium or in an organic solvent, for example,

benzene, pyridine, ether or alcohol, normally at a temperature between 0° and 25°C. The halide may be, for example, acetyl chloride, acetyl bromide, propionyl chloride, butyric chloride, benzoyl chloride and so on.

The N-amino-acyl-aminoacetonitrile used as a starting material in the process of the invention may itself be conveniently prepared by a sequence of reactions comprising (i) reacting aminoacetonitrile with a phthaloyl-amino-acid derivative so as to form N-phthaloyl-amino-acyl-aminoacetonitrile, (ii) which is then reacted with hydrazine or a derivative thereof so as to form the desired starting material. The phthaloyl-amino-acid derivative may be, for example, a halide, whilst the hydrazine derivative may be the hydrate.

The present invention extends, of course, to the N-(acyl-amino-acyl)-aminoacetonitriles, whenever prepared by a process substantially as herein described.

Moreover, the present invention extends, in a further aspect, to pharmaceutical compositions containing an N-(acyl-amino-acyl)-aminacetonitrile and an acceptable pharmaceutical vehicle therefor.

As used herein the phrase "acceptable pharmaceutical vehicle" embraces the wide variety of carriers which may be used for the presentation of the compounds of the invention, and may be regarded as having the following particular meanings in relation to the usual modes of administration.

a) So far as oral administration is concerned, the phrase means the injestible coherent solid excipient of a tablet, coated tablet, pill or sub-lingual tablet, the ingestible container of a capsule or cachet, the ingestible and usually flavoured pulverulent solid carrier of a powder, or the ingestible and again usually flavoured liquid medium of a syrup or elixir.

b) So far as administration by injection is concerned, the phrase means a sterile injectable liquid solution or suspension medium, the composition being desirably presented in single-dose ampoules or multi-dose containers.

c) So far as administration rectally is concerned, the phrase means a base material of low melting-point capable of releasing the active ingredient, which base material when appropriately shaped forms a suppository.

It is particularly preferred that the pharmaceutical compositions are in unit dosage form whereby the desired rate of administration for the compounds of the invention may be achieved by a single dose.

In order that the invention may be more fully understood, it will now be described, though only by way of illustration, with reference to the following Examples.

EXAMPLE 1:

N - (N - Acetyl - glycyl) - aminoacetonitrile.

1 g. of N-glycyl-aminoacetonitrile or its acetate is dissolved in 5 cc. of water, and 1.5 cc. of acetic anhydride is added with stirring at room temperature. After 15 minutes, another 1.5 cc. of acetic anhydride is added with stirring and the stirring is continued for 30 minutes thereafter. Condensation under reduced pressure is then effected. The residual crystals are subjected to recrystallization with ethanol, to give 0.8 g. of fine plate crystals of the desired product, melting point 157°—159°C.

Analysis:

Calculated: C: 46.44, N: 5.85, N: 27.08
Determined: 46.41, 5.67, 27.85

The N-glycyl-aminoacetonitrile used as a starting material in this example is produced by dissolving 5 g. of aminoacetonitrile sulphate in 100 cc. of water, adding 12 g. of sodium bicarbonate, cooling the resulting solution to 5°C, and adding 50 cc. of a dioxan solution containing 10 g. of phthaloyl glycyl chloride dropwise with stirring over a period of 30 minutes, crystals being precipitated during this period. The whole is stirred at 5°C for 2 hours, and the crystals are collected by filtration, washed with water, and dried. White needle crystals of phthaloyl glycyl-aminoacetonitrile are obtained by recrystallization from acetonitrile, the melting point of the crystals being 245°—246°C.

Analysis: $C_{12}H_9O_3N_3$

Calculated: N: 17.28
Determined: 17.57

7 g. of the phthaloyl glycyl-aminoacetonitrile are added to 50 cc. of an alcoholic solution containing 18 g. of 80% hydrazine hydrate, and the whole is heated for 1.5 hours to distil off the alcohol under reduced pressure. The residue is added to 70 cc. of an aqueous solution containing 75 g. of concentrated hydrochloric acid, and the solution is stirred for 5 minutes and cooled. The undissolved crystals are filtered off and then the solution is condensed at 40°C so that a syrup-like residue is obtained. This is dissolved in a minimal amount of methanol, and the solution is left in a refrigerator. 3 g. of white crystals of the desired starting material are obtained. The melting point of the substance is between 179°—183°C.

Analysis: $C_4H_{10}N_3Cl$.

Calculated: N, 28.05
Determined: N, 28.87

EXAMPLE 2:

N - (N - Acetyl - glycyl) - aminoacetontrile

1 g. of glycyl-aminoacetonitrile acetate is dissolved in 5 cc. of water, and 2 g. of sodium bicarbonate are added. 1 cc. of an ether solution of 0.5 g. of acetyl chloride are added dropwise to the solution at a temperature between 0° and 5°C while stirring and with cooling of the solution with iced water. The stirring is continued at a temperature between

0°—5°C for 30 minutes thereafter, and then at room temperature for a further hour. The reaction solution is filtered and, when the filtrate is subjected to condensation under reduced pressure below 40°C, there are obtained crystals which are extracted with hot ethanol. The undissolved materials are filtered off. When the filtrate is cooled, 0.6 g. of white plate crystals of the desired product are obtained.

The melting point of the product is 157°—159°C. When it is mixed with the product obtained in Example 1, no lowering of the melting point is observed.

EXAMPLE 3:

N - (N - Benzoyl - glycyl) - aminoacetonitrile

1.1 g. of N-glycyl-aminoacetonitrile acetate are dissolved in 10 cc. of water, 1.7 g. of sodium bicarbonate are added to the solution, and the mixture is cooled to 0° to 5°C by ice. 0.9 g. of benzoyl chloride are then added, and crystals are precipitated from the solution. After four hours the precipitated crystals are collected by filtration, washed with cold water and, when recrystallized with ethanol, give 1.2 g. of white needle crystals of the desired product, melting point 186°—188°C.

Analysis:

Calculated:	C: 60.82,	H: 5.10,	N: 19.35
Determined:	60.46,	4.86,	19.53

EXAMPLE 4:

N - (N - Acetyl - valyl) - aminoacetonitrile

500 mg. of N-valyl-aminoacetonitrile acetate are dissolved in 5 cc. of water, and the solution is treated with 0.75 cc. of acetic anhydride added in two portions in a manner similar to that used in Example 1. The resulting crystals are recrystallized with hot water, and 420 mg. of white needle crystals having a melting point between 187°—188° C are obtained. Infra-red analysis (wave number cm^{-1});

νNH: 3380, 3020; νC=O: 1670, 1650

δNH: 1530, 1550 δ_s CH_3: 1380; $\delta(CH_3)_2$ CH: 1160

These measurements indicate that the crystals are the desired product.

EXAMPLE 5:

N (N - Benzoyl - valyl) - aminoacetonitrile

4.5 g. of the desired product are obtained by reacting 0.5 g. of N-valyl-aminoacetonitrile acetate with benzoyl/chloride in a manner similar to that described in Example 3. The white needle crystals which are obtained are recrystallized from ethanol and have a melting point between 225°—227°C (by capillary tube). When the melting point is determined by micro-analysis, the crystals begin to sublimate gradually about 200°C, and show a melting point of 234°C.

Analysis:

Calculated:	C, 64.84;	H, 6.61;	N, 16.21
Determined:	64.68;	6.41;	16.54

EXAMPLE 6:

N - (N - Benzoyl - leucyl) - aminoacetonitrile

200 mg. (0.00087 mole) of N-leucyl-aminoacetonitrile acetate are dissolved in 2 cc. of water, 160 mg. (0.002 mole) of sodium bicarbonate are added, and then 1 cc. of an ether solution of 210 mg. of benzoyl chloride is added. Upon vigorous stirring, crystals begin to precipitate. 3 cc. of ether is then added and, after stirring for 30 minutes, the crystals are collected by filtration and recrystallized from water-alcohol. The white needle crystals of the desired product which are obtained have a melting point between 158—159°C.

Analysis:

Calculated:	C, 65.91;	H, 7.01;	N, 15.37
Determined:	66.38;	6.91;	15.49

EXAMPLE 7:

N (N - Benzoyl - α - alanyl) - aminoacetonitrile

200 mg. of N-α-alanyl-aminoacetonitrile are dissolved in 2 cc. of water, 200 mg. of sodium bicarbonate are added thereto, and then 200 mg of benzoyl chloride dissolved in 3 cc. of ether are added. The whole is stirred vigorously at room temperature, and is then left overnight. The resulting crystals are collected by filtration, and recrystallized from hot water (containing active carbon), to give 210 mg. of white needle crystals of the desired product.

Analysis:

Calculated:	C, 62.32;	H, 5.67;	N, 18.17
Determined:	62.24;	5.37;	18.61

EXAMPLE 8:

N - (N - Acetyl - α - alanyl) - aminoacetonitrile

100 mg. of N-α-alanyl-aminoacetonitrile acetate and 0.15 cc. of acetic anhydride are reacted and treated in a manner similar to that described in Example 1 to give the desired product. Recrystallized from isopropyl alcohol, 60 mg. of white needle crystals of the product, having a melting point between 149°—150°C, are obtained.

Infra-red analysis (cm^{-1}): νNH: 3380, 3300, νC=O: 1680, 1640.

δNH: 1570, 1540

$\delta_s CH_3$ 1380, 1260.

Thus the crystals are determined to be the desired product.

EXAMPLE 9:

N - [N - (N - Benzoyl - ξ - amino - caproyl) - glycyl]-aminoacetonitrile

Sodium bicarbonate is added to an aqueous solution of N-glycyl-aminoacetonitrile acetate, and an ether solution of N-benzoyl-ξ-aminocaproic acid is then added, with stirring, at

5°C. The stirring is continued at the same temperature for 3 hours, and then at room temperature for 8 hours, until the odour of the chloride disappears. The crystals which are obtained are recrystallized from alcohol or hot water, and white needle crystals of the desired product, having a melting point between 158°—160°C, are obtained.

Analysis:

Calculated: N: 16.96
Determined: 17.26

EXAMPLE 10:

In a manner essentially similar to that described above, the following compounds are obtained:

(a) White needle crystals of N-(N-propionyl-glycyl)-aminoacetonitrile, melting point between 159°—160°C, using ethanol as the recrystallization solvent.

(b) White needle crystals of N-(N-n-butyryl-glycyl)-aminoacetonitrile (m.p. 129°—131°C), recrystallizing from ethanol.

(c) White plate crystals of N-(N-n-caproyl-glycyl)-aminoacetonitrile (m.p. 142°—143°C), recrystallizing from ethanol.

(d) White plate crystals of N-(N-n-heptanoyl)-glycyl)-aminoacetonitrile (m.p. 141—141.5°C), recrystallizing from water-ethanol.

(e) White plate crystals of N-(N-n-caprylyl-glycyl)-aminoacetonitrile (m.p. 146°—147°C), recrystallizing from ethanol.

(f) White needle crystals of N-(N-acetyl-alanyl)-aminoacetonitrile (m.p. 149°—150°C) recrystallizing from isopropyl alcohol.

(g) White needle crystals of N-(N-benzoyl-alanyl)-aminoacetonitrile (m.p. 168°C), recrystallizing from water.

(h) White needle crystals of N-(N-isobutyryl-alanyl)-aminoacetonitrile (m.p. 165°—166°C), recrystallizing from ethanol.

(i) White needle crystals of N - (N - propionyl-valyl)-aminoacetonitrile (m.p. 184°—185°C), recrystallizing from ethanol.

(j) White needle crystals of N-(N-butyryl-valyl)-aminoacetonitrile (m.p. 172°—173°C), recrystallizing from 30% ethanol.

(k) White needle crystals of N-(N-isobutyryl-valyl)-aminoacetonitrile (m.p. 192°—193°C), recrystallizing from ethanol.

(l) White needle crystals of N-(N-n-caproyl-valyl)-aminoacetonitrile (m.p. 167°—168°C), recrystallizing from ethanol.

(m) White needle crystals of N-(N-n-heptanoyl-valyl)-aminoacetonitrile (m.p. 167°—168°C), recrystallizing from ethanol.

(n) White plate crystals of N-(N-n-caprylyl-valyl)-aminoacetonitrile (m.p. 148°—149°C), recrystallizing from water-ethanol.

(o) White prism crystals of N-(N-acetyl-leucyl)-aminoacetonitrile (m.p. 144°—145°C), recrystallizing from acetonitrile.

(p) White needle crystals of N-(N-propionyl-leucyl)-aminoacetonitrile (m.p. 127°—128°C), recrystallizing from water.

(q) White needle crystals of N-(N-isobutyryl-leucyl)-aminoacetonitrile (m.p. 134°—135°C), recrystallizing from water.

(r) White needle crystals of N-(N-acetyl-β-alanyl)-aminoacetonitrile (m.p. 143°—144°C), recrystallizing from ethanol.

(s) White plate crystals of N-(N-acetyl-ε-aminocaproyl)-aminoacetonitrile (m.p. 103°—104°C), recrystallizing from ethyl acetate.

(t) White needle crystals of N-(N-acetyl-α-aminocaproyl)-aminoacetonitrile (m.p. 147°C), recrystallizing from ethyl acetate.

(u) White needle crystals of N-(N-acetyl-δ-aminocaproyl)-aminoacetonitrile (m.p. 88°—92°C), recrystallizing from ethyl acetate.

(v) White leaflet crystals of N-(N-acetyl-α-aminobutyryl)-aminoacetonitrile (m.p. 94°—96°C), recrystallizing from ethyl acetate.

(w) White needle crystals of N-(N-acetyl-methionyl)-aminoacetonitrile (m.p. 109°—111°C), recrystallizing from isopropyl-alcohol.

(x) White prism crystals of N-(N-acetyl-tryptophyl)-aminoacetonitrile (m.p. 196°—197°C), recrystallizing from acetic acid.

(y) White needle crystals of N-(N-acetyl-asparaginyl)-aminoacetonitrile (m.p. 195°—196°C), recrystallizing from water-ethanol.

(z) White needle crystals of N-(N-i-valeryl-methionyl)-aminoacetonitrile (m.p. 101°—102.5°C), recrystallizing from water.

(a') White needle crystals of N-(N-acetyl-phenylalanyl)-aminoacetonitrile (m.p. 188°—189°C), recrystallizing from water-ethanol.

(b') White needle crystals of N-(N-acetyl-O-acetyl-tyrosyl)-aminoacetonitrile (m.p. 179°—180°C), recrystallizing from water.

(c') White needle crystals of N-(N-acetyl-phenyl-glycyl)-aminoacetonitrile (m.p. 192°—193°C), recrystallizing from acetonitrile.

(d') White leaflet crystals of N-(N-acetyl-δ-aminovaleryl)-aminoacetonitrile (m.p. 101°C), recrystallizing from ethyl acetate.

WHAT WE CLAIM IS:—

1. N-(Acyl-amino-acyl)-aminoacetonitriles of the general formula:

$$R^1.CO.NH.R.CO.NH.CH_2.CN$$

wherein HN.R.CO is the basic structure of amino-acids $H_2N.R.COOH$, and R is a substituted or unsubstituted hydrocarbon group, and R^1 is a straight or branched alkyl, aryl or aralkyl group.

2. N-(Acyl-amino-acyl)-aminoacetonitriles as claimed in claim 1, wherein the group HN.R.CO is derived from glycine, α-alanine, β-alanine, α-aminobutyric acid, α-amino-isobutyric acid, valine, leucine, isoleucine, norleucine, methionine, lysine, tryptophane, α,β,γ,δ or ε-aminocaproic acid, aspartic acid, phenyl-alanine, tyrosine, phenyl-glycine or δ-amino-valeric acid.

3. N-(Acyl-amino-acyl)-aminoacetonitriles as claimed in claim 1 or claim 2, wherein the group R^1 contains from 1 to 9 carbon atoms.

4. N - (Acyl - amino - acyl) - aminoacetonitriles as claimed in claim 3, wherein the group R^1 is the methyl, ethyl, propyl, i-propyl, butyl, pentyl, hexyl or benzyl group.

5. N-(N-Acetyl-glycyl)-aminoacetonitrile.

6. N-(N-Benzoyl-glycyl)-aminoacetonitrile.

7. N-(N-Acetyl-valyl)-aminoacetonitrile.

8. N(N-Benzoyl-valyl)-aminoacetonitrile.

9. N-(N-Benzoyl-leucyl)-aminoacetonitrile.

10. N - (N - Benzoyl - α - alanyl) - amino - acetonitrile.

11. N - (N - Acetyl - α - alanayl) - amino - acetonitrile.

12. N-(N-(N-Benzoyl -ε- amino-caproyl)-glycyl)-aminoacetonitrile.

13. N - (N - Propionyl - glycyl) - amino - acetonitrile.

14. N - (N - n - Butyryl - glycyl) - amino - acetonitrile.

15. N - (N - n - Caproyl - glycyl) - amino - acetonitrile.

16. N - (N - n - Heptanoyl - glycyl) - aminoacetonitrile.

17. N - (N - n - Caprylyl - glycyl) - aminoacetonitrile.

18. N - (N - Acetyl - alanyl) - amino - acetonitrile.

19. N - (N - Benzoyl - alanyl) - amino - acetonitrile.

20. N - (N - iso - Butyryl - alanyl) - amino - acetonitrile.

21. N - (N - Propionyl - valyl) - amino - acetonitrile.

22. N - (N - Butyryl - valyl) - amino - acetontrile.

23. N - (N - iso - Buturyl - valyl) - amino - acetonitrile.

24. N - (N - n - Caproyl - valyl) - amino - acetonitrile.

25. N - (N - n - Heptanoyl - valyl) - aminoacetonitrile.

26. N - (N - n - Caprylyl - valyl) - amino - acetonitrile.

27. N - (N - Acetyl - leucyl) - amino - acetonitrile.

28. N - (N - Propionyl - leucyl) - amino - acetonitrile.

29. N - (N - iso - Butyryl - leucyl) - aminoacetonitrile.

30. N - (N - Acetyl - β - alanyl) - amino - acetonitrile.

31. N - (N - Acetyl - ε - aminocaproyl) - aminoacetonitrile.

32. N - (N - Acetyl - α - aminocaproyl) - aminoacetonitrile.

33. N - (N - Acetyl - δ - aminocaproyl) - aminoacetonitrile.

34. N - (N - Acetyl - α - aminobutyryl) - aminoacetonitrile.

35. N - (N - Acetyl - methionyl) - amino - acetonitrile.

36. N - (N - Acetyl - tryptophyl) - amino - acetonitrile.

37. N - (N - Acetyl - asparaginyl) - amino - acetonitrile.

38. N - (N - iso - Valeryl - methionyl) - aminoacetonitrile.

39. N - (N - Acetyl - phenylalanyl) - aminoacetonitrile.

40. N - (N - Acetyl - O - acetyl - tyrosyl) - aminoacetonitrile.

41. N - (N - Acetyl - phenyl - glycyl) - aminoacetonitrile.

42. N - (N - Acetyl - δ - aminovaleryl) - aminoacetonitrile.

43. A method for preparing an N-(acyl-amino-acyl)-aminoacetonitrile as claimed in any of claims 1 to 42, comprising reacting an N-amino-acyl-aminoacetonitrile with an acylating agent so as to form the corresponding N-acyl-amino-derivative.

44. A method as claimed in claim 43, wherein the acylating agent is an acid anhydride.

45. A method as claimed in claim 44, wherein the reaction is effected in an aqueous medium.

46. A method as claimed in claim 44 or claim 45, wherein the anhydride is acetic, propionic, butyric, or isobutyric anhydride.

47. A method as claimed in claim 43, wherein the acylating agent is an acyl halide.

48. A method as claimed in claim 47, wherein the halogen atom in the halide is chlorine or bromine.

49. A method as claimed in claim 47 or claim 48, wherein there is an acid binding agent present in the reaction mixture.

50. A method as claimed in claim 49, wherein the acid binding agent is sodium bicarbonate, sodium carbonate, potassium carbonate, pyridine or triethylamine.

51. A method as claimed in any of claims 47 to 50, wherein the reaction is effected in an aqueous medium or in an organic solvent.

52. A method as claimed in claim 51, wherein the solvent is benzene, pyridine, ether or alcohol.

53. A method as claimed in any of claims 47 to 52, wherein the reaction is effected at a temperature between 0° and 25°C.

54. A method as claimed in any of claims 47 to 53, wherein the halide is acetyl chloride, acetyl bromide, propionyl chloride, butyryl chloride or benzoyl chloride.

55. A method as claimed in any of claims 43 to 54, wherein the N-amino-acyl amino-acetonitrile starting material is in the form of its acetate.

56. A method as claimed in any of claims 43 to 55, wherein the N-amino-acyl-amino acetonitrile starting material is prepared by a sequence of reactions comprising (i) reacting aminoacetonitrile with a phthaloyl-amino-acid derivative so as to form N-phthaloyl-amino-acyl-aminoacetonitrile, (ii) which is then reacted with hydrazine or a derivative thereof so as to form the desired starting material.

57. A method as claimed in claim 56,

wherein the phthaloyl-amino-acid derivative is a halide.

58. A method as claimed in claim 56 or claim 57, wherein the hydrazine derivative is the hydrate.

59. A method as claimed in any of claims 43 to 58, substantially as herein described.

60. A method for preparing an N-(acyl-amino-acyl)-aminoacetonitrile as claimed in any of claims 1 to 42, substantially as hereinbefore described, particularly with reference to any of the foregoing Examples.

61. An N-(acyl-amino-acyl)-aminoacetonitrile, whenever prepared by a process as claimed in any of claims 43 to 60.

62. A pharmaceutical composition containing an N-(acyl-amino-acyl)-aminoacetonitrile as claimed in any of claims 1 to 42 and 61 and an acceptable pharmaceutical vehicle therefor.

63. A pharmaceutical composition as claimed in claim 62, wherein the vehicle is the ingestible coherent solid excipient of a tablet, coated tablet, pill or sub-lingual pill, the ingestible container of a capsule or cachet, the ingestible carrier of a powder, or the ingestible liquid medium of a syrup or elixir.

64. A pharmaceutical composition as claimed in claim 62, wherein the vehicle is a sterile injectable liquid solution or suspension medium.

65. A pharmaceutical composition as claimed in claim 62, wherein the vehicle is a base material of low melting point capable of releasing the nitrile, which base material when appropriately shaped forms a suppository.

66. A pharmaceutical composition as claimed in any of claims 62 to 65, substantially as herein described.

For the Applicants,
SANDERSON & CO.,
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1073288 COMPLETE SPECIFICATION
1 SHEET This drawing is a reproduction of the Original on a reduced scale

Figure 1. TENDENCY OF GLUTAMIC OXAROACETIC TRANSAMINASE IN BLOOD SERUM

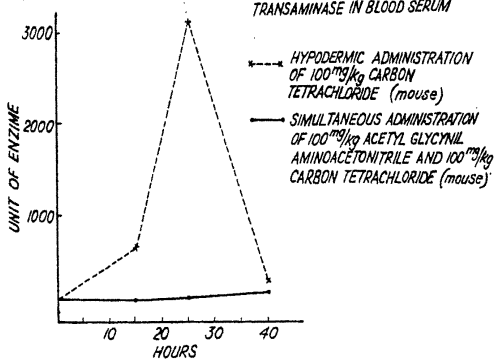

Figure 2. TENDENCY OF GLUTAMIC PYRUVIC TRANSAMINASE IN BLOOD SERUM